REMARKS

Rejection under 35 USC §103

Claims 1-4, 6-13, 12 and 15-18 have been rejected under 35 USC §103(a) as being anticipated by Richardson et al. (US 5,490,980) in view of Green et al. (US 5,525,336); Kanebo Ltd. (JP 02-204407, abstract) Dane, Hair Chemistry 1, and the record for transglutaminase from BRENDA. This rejection is identical to that of the previous office action. The Examiner's comments consist primarily of response to Applicants' arguments in rebuttal of the previous rejection. In brief, Applicants' invention, in its broadest embodiment, is a method for retaining or imparting curl to hair or eyelashes by contacting the hair or lashes with a composition containing the enzyme transglutaminase. In Applicants' previous response, Applicants noted the following flaws, both technical and legal, in the Examiner's basis for the rejection:

1. Richardson does not disclose any *in situ* crosslinking of glutamine or lysine residues within a hair strand by any means, but rather discloses the crosslinking of an active containing a an alkylamine moiety, externally applied, to skin or hair. Because the intent of the invention is to attach an external agent to a glutamine or lysine residue on the skin or hair, the teaching of the document read as a whole teaches that crosslinking within a strand would be undesirable, as doing so would render these residues unavailable to accept the external agent for crosslinking.
2. Green expressly teaches the use of transglutaminase to link lysine and glutamine residues in different proteins, not the same proteins, as would be the case in linking residues within keratin, the purpose said to be the formation of a "protective layer" on skin.
3. The Kanebo teachings are not at all clear with regard to what is being done, although like Green, it does refer to formation of a "protective layer" which leads to moisture retention by the hair. As is known to anyone with curls, moisture is anathema to curl retention. Whatever if may be that Kanebo is teaching, it unequivocally does not teach the use of transglutaminase to link amino acid residues within keratin strands, nor that doing so can aid in retaining or imparting curl to hair.
4. Danes teaches nothing regarding glutaminase at all, but merely discusses various types of bonds that occur in hair. It is noted in Danes that the only type of bond that has any durability is a disulfide bond. The bond between glutamine and lysine is notably not a disulfide bond, and therefore, not only is Danes not relevant to the process of the present invention, it actually shows how unexpected the curl retention that occurs between glutamine and lysine actually is.

5. The BRENDA reference only teaches a collection of information relating to the properties of various transglutaminase enzymes. Utterly absent from this disclosure is a disclosure of the use of transglutaminase to curl hair or to crosslink amino acids within a hair strand, or under what conditions transglutaminase might be used on the hair to achieve this undisclosed and unexpected result.

In response to Applicants arguments as summarized above, the Examiner has provided a lengthy analysis which actually fails to rebut any of noted flaws in the basis for the rejection. For example, regarding Applicants' comments on the Richardson reference, the Examiner states:

> Applicants have read the reference too narrowly, particularly as the rejection is a combination of teachings of the cited references. Richardson et al. disclose applying a composition comprising an effective amount of transglutaminase to hair. Although the composition comprises other compounds, nothing in the composition, or in the process of applying the composition to hair, restricts the enzyme to reacting only with the alkylamine compound or compounds. The enzyme acts on both the alkylamine-containing compound(s) and on hair. Alkylamine groups in the other compound(s) and lysine residues in keratin molecules are bound to glutamine residues. It is clear from the previous Office action that BRENDA was cited because it teaches the transglutaminase reaction between lysine and glutamine residues.

Applicants do not necessarily disagree with certain of the Examiner's statements. It has never been Applicants' contention that the target reaction of transglutaminase between glutamine and lysine residues is unknown; it is clearly stated in the literature. What is not stated anywhere, in either Richardson or any of the other cited references, is that activity can be exploited to retain curl in hair. Indeed, there is nothing in any reference cited by the Examiner that suggests that the crosslinking of lysine and glutamine residues in keratin, even if it does occur, would result in any effect on the hair's curling. Applicants have in fact reviewed the article (Chung and Folk) cited in Puszkin et al. pointed to by the Examiner as stating that transglutaminase has been postulated to crosslink keratin. A careful review of the article shows that transglutaminase mentioned is in fact a naturally and normally occurring component in the hair, and that it "catalyze[s] the incorporation of primary amines into peptides and proteins" (page 306). Clearly, since all hair appears to contain this transglutaminase, the article later (page 307) notes that the enzyme may be partially responsible for the formation of ε(γglutamyl)lysine crosslinks in hair proteins. Neither of these citations makes any reference to such links being responsible for hair curl; in fact, other references have referred to this crosslinking as being responsible for the stiffening of the cuticle of the keratin fiber (see Swift and Smith reference, accompanying this amendment). Indeed, since all hair appears to naturally possess this enzyme, and glutamyl-lysine

crosslinks, and the majority of hair is *not* curly, then there are obviously glutamine-lysine interactions that do not result in hair curling. In fact, Applicants are not even certain that this is the means by which the observed effect occurs; they have simply demonstrated an unexpected effect, and postulated a possible explanation. It is the Examiner who has presumed to make this the basis of the rejection, with no evidence whatsoever found in the prior art. If crosslinking between glutamine and lysine in a keratin fiber is even part of the basis for hair curling, Applicants appear to be the first to have observed the effect and to have proposed a theory for it.

This fundamental problem with the premise of the Examiner's rejection being established above, Applicants further note that the Examiner's position that there is nothing in the composition or the process to restrict the enzyme reacting only with the alkylamine compounds and that the enzyme acts on both the alkylamine compounds and hair, and thus, to take that assumption one step further into legal terms, the practice of the process would by inherency achieve crosslinking of lysine and glutamine residues in hair. This argument fails on two grounds, one technical and one legal. First, the very nature of the components of the process of Richardson are calculated to prevent the reaction between lysine and glutamine residues within the hair strand, because the alkylamine compounds are targeted to the glutamine residues on hair, and therefore compete with the lysine residues for binding with glutamine. Presumably, if indeed the method of Richardson works for its intended purpose, this competition is effective, because otherwise there would be little or no binding of the alkylamine moiety to a glutamine residue, since, under the Examiner's theory, they would all be occupied by crosslinking with lysine residues, and thus unavailable for binding. Again, to quote the express intention of Richardson, as cited in the first sentence of column 11, "Transglutaminase is employed ...in an amount effective to crosslink the active ingredient to glutamine residues in human skin, hair or nails". Crosslinking of glutamine to lysine residues within the hair is clearly not intended, and all evidence provided in the document supports this, i.e., that the alkylamine modified compounds do get crosslinked to glutamine residues, and *in situ* lysine residues do not.

As to the legal failure of the Examiner's position, the question to be asked is, would there a remote possibility that a stray lysine residue may coincidentally link to a glutamine residue in the presence of transglutaminase? The possibility cannot of course be conclusively eliminated, although nothing in the reference suggests such an occurrence. However, even if such an event might occur, it is clearly nothing more than an unintended consequence of practice of the process, and at best incidental to the main result. Such an unintended, and clearly unappreciated, consequence cannot form the basis of an assertion of inherency. Inherency may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient to establish inherency that can form the basis of a rejection of patent claims. *In re Oelrich and Divigard,* 212 USPQ 323 (CCPA

1981). Thus, even if the linking of glutamine and lysine residues should accidentally occur, such occurrence would not be adequate to support the present rejection.

In addressing Applicants' rebuttals regarding the teachings of Richardson, the Examiner asserts that Applicants have read the reference too narrowly, noting that the rejection is based on a combination of references. While that is of course true, Richardson is the primary reference cited by the Examiner, and as such forms the crux of the rejection. Applicants' demonstration of the incorrectness of the PTO's analysis of Richardson, and the fundamental, but flawed premise on which it is based, eliminates a critical element of the basis for the obviousness rejection, and cannot be dismissed as an inappropriate focus on a single reference in a combination of references. Applicants have shown that Richardson does not teach or suggest, either expressly or inherently, that transglutaminase was useful in crosslinking human keratin proteins, let alone teach that it is useful in crosslinking lysine and glutamine residues in hair in such a way as to affect curl in hair. Therefore, it fails in the purpose for which it was originally cited.

Without the teaching of Richardson on which the PTO's rejection of the present claims is founded, Green does not provide any further teaching that would remedy the defect in the rejection. In the present office action, the Examiner states:

> [I]t is clear that Green et al. were cited because they teach that transglutaminase is a cross-linking agent that cross-links corneocyte proteins that are present in the stratum corneum of the skin, hair or nails...Green teaches that transglutaminase alone may be applied to hair and that it cross-links hair. It is clear that Green et al. were not cited for the specific compounds that they disclose.

Applicants are in agreement that the identity of the compounds disclosed in Green is not the issue. However, it is unclear why the Examiner believes that, even if Green does teach that transglutaminase can crosslink hair (which Applicants do not agree is the teaching of Green), why that teaching suggest that transglutaminase can be used to retain curl in hair. There is nothing in Green, or any of the other cited references, that suggests that such an activity would result in any effect on the curling of hair. Again, if the Examiner is impliedly relying on an inherency argument, this reliance is misplaced. Green does show that corneocyte proteins can be crosslinked to skin cells by transglutaminase; Green does not disclose anywhere that transglutaminase actually can crosslink hair, or even provide an example of application of transglutaminase to hair. Therefore, there is no inherent disclosure of the crosslinking of hair to be found in Green. More importantly, however, the sole teaching that can be found that approximates the Examiner's position is that transglutaminase <u>may</u> crosslink certain corneocyte proteins that are in skin, hair or nails; this does not translate, either alone, or in combination with any other cited reference, to a suggestion of use in affecting the curl of hair, and as

shown above with respect to the Swift & Smith reference, the end result of this may be no more than a strengthening of the keratin fiber.

The PTO's rebuttal position with regard to Kanebo is stated in the present office action as follows:

> [T]he abstract discloses that 'The TGase catalyzes the reaction of free glutamine residue and lysine residue existing in the outermost layer of the hair to forma crosslinking consisting of ε-(γ-glutamine)lysine bond. Accordingly, the surface is densified, the damaged hair, the water-retainability and the moisture-retainability of hair are improved and the hair is imparted with gloss, softness and springiness.' Thus, Kanebo teaches the application of transglutaminase to hair to cross-link it. Springiness is curl, straight hair is not springy. Applicants assert that water retention is not the purpose of the instant invention. But water retention occurs during conditioning, which is a moisturizing treatment, and which is the subject of withdrawn claim 19.

The Examiner's position on the teachings of the Kanebo reference are insupportable. In fact, the statements made by the Examiner are sweeping conclusions absolutely uncorroborated either by any evidence on record, or on general knowledge available in the art. Particularly outrageous is the Examiner's conclusion that "springiness is curl; straight hair is not springy". First, Applicants request that the Examiner provide even an iota of support for the statement that "springiness" is equivalent in definition to "curl". The Examiner cannot randomly assign a meaning to a word, without support, simply because such a meaning will support her rejection. A casual investigation of the meanings of the word "springy" as it is defined and understood by the average person, include "flexible", "elastic" or "bouncy". In one record found on the Internet, it even likens it, in terms of hair, to "clean, bouncy hair"(copy attached). Nowhere in the many other suggested definitions is "curly" found. The statement that straight hair is not springy is equally untenable. The clear meaning of "springy" is the ability to stretch and rebound without breaking after being pulled. This is a desirable characteristic of all hair, and obviously can be applied to healthy hair of any type. This is further supported by the accompany excerpt from the P&G *The World of Hair* segment on "Elasticity"; this excerpt even refers to elasticity as "spring". Hair care companies would be hard pressed for business if their only option for selling products advertised as imparting bounce and flexibility was limited to the minority of customers with curly hair. Obviously, both curly and straight hair can exhibit spring, within the normally understood meaning of that word. That the meaning of the word in the context of the Kanebo document is intended to apply to other than just curly hair is further borne out by the fact that Kanebo is a Japanese company, selling primarily in Asian markets, where straight hair is virtually universal. It is highly unlikely that the document in question, therefore, is intended to refer solely to curled hair.

Moreover, the abstract cited does not provide any details of how the transglutaminase is applied to hair, or in what amounts; it therefore cannot be presumed that the application disclosed in Kanebo

inherently would result in curl retention. Indeed, as noted above, the linking of glutamine and lysine residues is not necessarily associated with curl induction, as the natural occurrence of transglutaminase in all types of hair is indicative of the natural role being strengthening of the keratin strand. Indeed, the statement in Kanebo, that the surface structure is "densified", much more clearly supports this interpretation of the function of crosslinking of glutamine and lysine residues. Finally, the Examiner notes, in response to Applicants' assertion that water retention is not only not the purpose of the invention, but also tends to defeat curl retention, that water retention occurs during conditioning, which is a moisturizing treatment, and with is the subject of withdrawn claim 19. It is Applicants' position that conditioning is not fairly equated with "moisturizing", but in any case, a discussion of that point is irrelevant, since the Examiner has pointed to a claim which is not even being considered in the present prosecution. However, in conclusion, it is reasonable to conclude, from a fair reading of the words of the Kanebo abstract, that there is neither an express nor inherent teaching of curl retention by application of transglutaminase in this document.

In responding to Applicants' arguments regarding Dane's failure to teach any involvement of glutamine-lysine bonds in hair curling, the Examiner has stated:

> ...Dane discusses disulfide bonds, ionic bonds and hydrogen bonds and teaches that disulfide bonds are broken and rearranged to perm hair. Ionic bonds and hydrogen bonds are broken when the hair is wetted, reform when the hair is dried and may be used to change the shape of hairs by rolling it wet and blowing it dry. Dane does not discuss covalent bonds. But it is clear in the previous Office action that Dane was cited because he or she teaches that the hair is permed by applying a cross-linking agent to create a new pattern, curly. One of ordinary skill in the art at the time the invention was made would have been motivated to design a product to maintain or enhance the curl of permed hair that contains an ingredient that can cross-link keratin, as disclosed by [cited references]., to maintain the new-crosslinking pattern in premed hair because Dane teaches that artificial curls can be created by cross-linking hair. Applicants assert that Dane renders completely unexpected and surprising the observation that a non-disulfide bond would have any ability to curl hair. But that Dane does not discuss bonds between lysine and glutamine residues has nothing to do with whether or not this observation is unexpected or surprising....It is the cross-linking that changes the shape of the strands, not the linkage of cysteine residues versus glutamine or lysine residues.

The Examiner's assertion that the character of the crosslink is irrelevant is quite incomprehensible. If the utter absence of anything relating to the ultimate point the Examiner is attempting to demonstrate is not relevant, it's not clear what would be. The only way in which to interpret the Examiner's position is that it assumes that every crosslinking of amino acids produces identical results, which is of course insupportable based on the disclosure of Dane, or any other disclosure of which Applicants are aware. The indiscriminate conclusion that any two crosslinks, regardless of the nature of the crosslink, or the amino acids between which the crosslinks occur, is seriously flawed on both legal and technical grounds. From a legal standpoint, the simple conclusory statement that Dane teaches

that any crosslinking of keratin results in curling of the hair is legally insufficient to support a conclusion of obviousness. The statement is made with no support whatsoever, and is not a piece of information that is part of the general knowledge in the art. In the present case, the Examiner has made a staggering leap of faith that, because crosslinking between two cysteine residues results in curled hair, the same must be true of crosslinking between lysine and glutamine residues. Such conclusory statements, with no backup or rationale (or at least no rationale based on science) has been expressly prohibited as a basis for rejecting a patent claim. *In re Lee,* Fed Cir. 61 USPQ 2d 1430 (Fed. Cir. 2002). See also *In re Zurco*, 59 USPQ 2d 1693 (Fed. Cir. 2001).

From a technical standpoint, however, the Examiner's position is obviously untenable as well. First, as is well known in the art, disulfide bonds form crosslinks in <u>all</u> hair types, not just curly hair (see Voet & Voet reference accompanying this amendment;). Disulfide bonds act to strengthen the keratin strand (see accompanying references from P&G, *The World of Hair,* section on "Hair Strength"; Proteomics and Genomics; and Arai et al., all showing that crosslinking resulting from disulfide bonds in hair produces mechanical strength and stability), but do not in themselves cause curl formation: as the Voet reference makes clear, it is the <u>disruption</u> of disulfide bond, followed by stretching the hair into a new shape, then <u>reformation</u> of the disulfide bonds around the new shape, that results in the curling effect observed in perms. More interesting, however, is that the same technique is used to <u>straighten</u> curly hair. Clearly, then, neither the mere existence of disulfide bonds *per se*, nor the crosslinking of keratin, are the basis of curl formation, and any attempt to equate the simple formation of a crosslink directly with curl formation must fail. Thus, even if lysine and glutamine formed disulfide bonds (which of course they don't), one would not predict, simply by virtue of their crosslinking, that curls would form or be retained thereby. Therefore, not only is the Examiner's reading of the Dane reference impermissibly broad, but it is also technically without merit. If the crosslinking of sulfur-containing amino acids in itself does not cause hair to curl, one of ordinary skill in the art would never be led to conclude from Dane that any other crosslinking between amino acids, let alone that between lysine and glutamine, would cause curl formation or retention, particularly in the absence of forming a new shape around which the bonds could be formed. Thus, the premise used by the Examiner for Dane's relevance is false and provides no basis on which an obviousness rejection could be formed.

In summary, then, Applicants have shown that the prior art completely lacks a teaching that crosslinking of keratin *per se*, by any means, can cause curl or retain curl in hair, and more specifically, that crosslinking of lysine and glutamine by the action of transglutaminase can cause curl or retain curl in hair. Having shown that the Examiner's premises in citation of the references discussed above to be incorrect, and further in the absence of any teaching even remotely relevant to the use of transglutaminase in curling hair, Applicants respectfully request withdrawal of the rejection of claims 1-4, 6-13 and 15-18.

With respect to claims 5 and 14, there has been no reiteration of the rejection with respect to these claims, but at the same time, there is no indication of allowance either. Applicants can only be assumed that the Examiner has inadvertently failed to apply the E-Z Permanent Makeup reference, previously cited, in combination with the Richardson, Green, Kanebo, Dane and BRENDA references cited above, against these claims, as this is the only reference cited that has any relevance to eyelashes whatsoever. The Examiner does mention this reference in the office action, in response to Applicants' arguments as to the irrelevance of the reference to the patentability of a claim that covers the curling of eyelashes by application of transglutaminase. The Examiner states, in pertinent part:

> It is clear in the previous Office action that this reference was cited for its disclosure that eyelashes can be permed, similarly to head hair, not for its disclosure of specific ingredients. As previously discussed, in looking for a composition that can maintain or enhance the curl of eyelashes, one of ordinary skill in the art would have been motivated to use or adapt an enzyme that can maintain or enhance curl in hair. The references cited above disclose that transglutaminase can maintain or enhance the curl of hair.

Although there is no express rejection, it is believed the foregoing statement expresses what the basis of such a rejection would be. This is very simply addressed. As the arguments and supporting documents presented in response to the rejection addressed above clearly show, the "references cited above" do not in any way show that transglutaminase can maintain or enhance the curl of hair. In the absence of the crucial basis for the Examiner's rejection of any of the claims, including claims 5 and 14, the addition of the E-Z Permanent Makeup reference to the list does not provide any useful teachings, since the Examiner has acknowledged it is not cited for its disclosure of specific ingredients, and clearly does not disclose transglutaminase having any effect on curling hair of any type. Thus, any intended or implicit rejection of claims 5 and 14 also has no foundation, and must also be withdrawn.

CONCLUSION

In view of arguments presented herein, claims 1-18 are believed to be in condition for allowance, and prompt issuance of a Notice of Allowance is respectfully solicited. The Examiner is encouraged to contact the undersigned by telephone if it is believed that discussion will resolve any outstanding issues.

Respectfully submitted,

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